PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 213/75, 215/38, 215/46, A61K 31/47, 31/44 — A1

(11) International Publication Number: WO 94/18170

(43) International Publication Date: 18 August 1994 (18.08.94)

(21) International Application Number: PCT/EP94/00189

(22) International Filing Date: 25 January 1994 (25.01.94)

(30) Priority Data:
9302275.4 5 February 1993 (05.02.93) GB

(71) Applicant (*for all designated States except US*): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex 9EP TW8 (GB).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): FORBES, Ian, Thomson [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). HAM, Peter [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). MARTIN, Roger, Thomas [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). THOMPSON, Mervyn [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB).

(74) Agent: GIDDINGS, Peter, J.; Corporate Intellectual Property, SmithKline Beecham, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB).

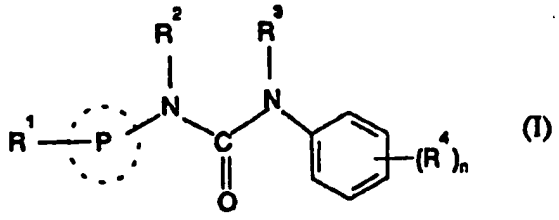
(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: USE OF PHENYL HETEROARYL UREAS AS $5HT_{2C}$ RECEPTOR ANTAGONISTS AND UREA COMPOUNDS

(57) Abstract

The use of a compound of formula (I) or a salt thereof, wherein P represents a quinoline or isoquinoline residue or a 5- or 6-membered aromatic heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur; R^1 is hydrogen, C_{1-6} alkyl, halogen, NR^5R^6 or OR^7 where R^5, R^6 and R^7 are independently hydrogen or C_{1-6} alkyl; R^2 and R^3 are independently hydrogen or C_{1-6} alkyl; R^4 is hydrogen, C_{1-6} alkyl, CF_3, nitro, cyano, acyl, halogen, NR^5R^6, OR^7 or CO_2R^7 where R^5, R^6 and R^7 are independently hydrogen or C_{1-6} alkyl as defined for R^1; and n is 1, 2 or 3, in the manufacture of a medicament for the treatment or prophylaxis of CNS disordres.



(I)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo			SE	Sweden
CH	Switzerland	KR	Republic of Korea	SI	Slovenia
CI	Côte d'Ivoire	KZ	Kazakhstan	SK	Slovakia
CM	Cameroon	LI	Liechtenstein	SN	Senegal
CN	China	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	[illegible]	TG	Togo
CZ	Czech Republic	LV	Latvia	TJ	Tajikistan
DE	Germany	MC	Monaco	TT	Trinidad and Tobago
DK	Denmark	MD	Republic of Moldova	UA	Ukraine
ES	Spain	MG	Madagascar	US	United States of America
FI	Finland	ML	Mali	UZ	Uzbekistan
FR	France	MN	Mongolia	VN	Viet Nam
GA	Gabon				

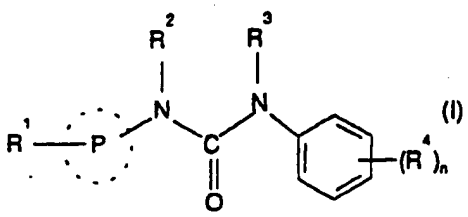
USE OF PHENYL HETEROARYL UREAS AS 5HT2C RECEPTOR ANTAGONISTS AND UREA COMPOUNDS

This invention relates to a method of treatment of certain CNS disorders.

WO 92/05170 describes certain urea derivatives which are described as possessing $5HT_{1C}$ receptor antagonist activity. The $5HT_{1C}$ receptor has recently been reclassified as the $5HT_{2C}$ receptor [P. Hartig et al., Trends in Pharmacological Sciences (TIPS) 1993].

Certain phenyl heteroaryl ureas known in the art have now been found to have $5HT_{2C}$ receptor antagonist activity. $5HT_{2C}$ receptor antagonists are believed to be of potential use in the treatment of CNS disorders such as anxiety, depression, obsessive compulsive disorders, migraine, anorexia, Alzheimers disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus.

Accordingly, the present invention provides the use of a compound of formula (I) or a salt thereof:



(I)

wherein:

P represents a quinoline or isoquinoline residue or a 5- or 6-membered aromatic heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur;

R^1 is hydrogen, C_{1-6} alkyl, halogen, NR^5R^6 or OR^7 where R^5, R^6 and R^7 are independently hydrogen or C_{1-6} alkyl;

R^2 and R^3 are independently hydrogen or C_{1-6} alkyl;

R^4 is hydrogen, C_{1-6} alkyl, CF_3, nitro, cyano, acyl, halogen, NR^5R^6, OR^7 or CO_2R^7 where R^5, R^6 and R^7 are independently hydrogen or C_{1-6} alkyl as defined for R^1; and

n is 1, 2 or 3,

in the manufacture of a medicament for the treatment or prophylaxis of CNS disorders.

C_{1-6}alkyl groups, whether alone or as part of another group, can be straight chain or branched.

Preferably R^1 is hydrogen or methyl.

Preferably R^2 and R^3 are hydrogen.

Suitable moieties when the ring P is a 5- or 6-membered aromatic heterocyclic ring include pyridyl, pyrazinyl, pyridazinyl, pyrimidinyl, isothiazolyl, isoxazolyl, thiadiazolyl and triazolyl. Preferably P is pyridyl attached to the urea nitrogen at position 3 or 4; or P is quinoline attached to the urea nitrogen at position 3, 4 or 6, preferably at position 4.

Preferably n is 1 or 2. When n is greater than 1, the R^4 groups can be the same or different. Preferably the phenyl ring is mono-substituted and R^4 is CF_3 or -NMe_2 (preferably in the meta position); -OMe, (preferably in the meta or para position); CO_2Et (preferably in the meta position) or the phenyl ring is preferably di substituted with meta chloro and para methyl.

Preferred compounds of formula (I) include:
N-(Phenyl)-N'-(2-methyl-4-quinolinyl) urea,
N-(6-Quinolinyl)-N'-(3-trifluoromethylphenyl) urea,
N-(3-Dimethylaminophenyl)-N'-(6-quinolinyl) urea,
N-(Phenyl)-N'-(6-quinolinyl) urea,
N-(4-Methoxyphenyl)-N'-(2-methyl-4-quinolinyl) urea,
N-(3-Dimethylaminophenyl)-N'-(2-methyl-4-quinolinyl) urea,
N-(3-Methoxyphenyl)-N'-(2-methyl-4-quinolinyl) urea,
N-(3-Ethoxycarbonylphenyl)-N'-(2-methyl-4-quinolinyl) urea,
N-(2-Methyl-4-quinolinyl)-N'-(3-trifluoromethylphenyl) urea ,
N-(Phenyl)-N'-(3-quinolinyl) urea,
N-(3-Chloro-4-methylphenyl)-N'-(3-pyridyl) urea,
N-(3-Chloro-4-methylphenyl)-N'-(4-pyridyl) urea,
N-(3-Pyridyl)-N'-(3-(trifluoromethyl)phenyl)urea,
N-(3-Methylphenyl)-N'-(3-pyridyl)urea,
N-(4-Chlorophenyl)-N'-(3-pyridyl)urea,
N-(3-Chlorophenyl)-N'-(3-pyridyl)urea,
N-(3-Hydroxyphenyl)-N'-(2-methyl-4-quinolinyl)urea,
N-(3-Bromophenyl)-N'-(3-pyridyl)urea,

N-(3,4-Dichlorophenyl)-N'-(3-pyridyl)urea,
N-(3-Fluoro-4-methylphenyl)-N'-(3-pyridyl)urea,
N-(4-Ethoxycarbonylphenyl)-N'-(3-pyridyl)urea,
N-(3-Chloro-4-methoxycarbonylphenyl)-N'-(3-pyridyl)urea,
N-(3-Bromo-4-methylphenyl)-N'-(3-pyridyl)urea,
N-(3-Chloro-4-cyanophenyl)-N'-(3-pyridyl)urea,
N-(4-Nitro-3-trifluoromethylphenyl)-N'-(3-pyridyl)urea,
N-(4-Chloro-3-trifluoromethylphenyl)-N'-(3-pyridyl)urea,
N-(3-Chloro-4-carboxyphenyl)-N'-(3-pyridyl)urea,
N-(2-Methoxy-4-trifluoromethylphenyl)-N'-(3-pyridyl)urea,
N-(3-Chloro-4-ethylphenyl)-N'-(3-pyridyl)urea,
N-(3-Chloro-4-propylphenyl)-N'-(3-pyridyl)urea,
N-(3-Chloro-4-tert-butylphenyl)-N'-(3-pyridyl)urea,
N-(3-Hydroxy-4-(methoxycarbonyl)phenyl)-N'-(3-pyridyl)urea
or a pharmaceutically acceptable salt thereof.

The compounds of the formula (I) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulphonic. Compounds of formula (I) may also form N-oxides or solvates such as hydrates, and the invention also extends to these forms.

Certain compounds of formula (I) may exist tautomerically in more than one form. The invention extends to these and any other tautomeric forms and mixtures thereof.
Certain compounds of formula (I) are capable of existing in stereoisomeric forms including enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis.

Certain compounds of formula (I) are novel and form a further aspect of the invention. Particularly preferred novel compounds include those listed above and exemplified herein.

The invention further provides a method of treatment or prophylaxis of CNS disorders, in particular anxiety, depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse, schizophrenia and/or disorders associated with spinal trauma and/or head injuries (in particular anxiety and depression) in mammals including humans, which comprises

administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The invention also provides novel compounds of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of anxiety, depression, migraine, anorexia, obsessive compulsive disorders, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse, schizophrenia and/or disorders associated with spinal trauma and/or head injuries.

The present invention also provides a pharmaceutical composition, which comprises novel compounds of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents

are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

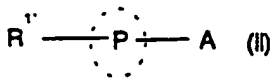
The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20.0 mg, for example 0.2 to 5 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.01 to 100 mg/kg; and such therapy may extend for a number of weeks or months.

When administered in accordance with the invention, no unacceptable toxicological effects are expected with the compounds of the invention.

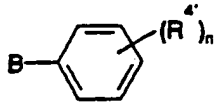
The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises

the coupling of a compound of formula (II);



(II)

with a compound of formula (III);



(III)

wherein P is as defined in relation to formula (I), A and B contain the appropriate functional group(s) necessary to form the moiety, $-NR^{2'}CONR^{3'}$ when coupled, the

variables $R^{1'}$, $R^{2'}$, $R^{3'}$, and $R^{4'}$ are R^1, R^2, R^3, and R^4 respectively, as defined in formula (I), or groups convertible thereto, and thereafter optionally and as necessary and in any appropriate rder, converting any $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$, when other than R^1, R^2, R^3 and R^4 respectively to R^1, R^2, R^3 and R^4, interconverting R^1, R^2, R^3, and R^4 and forming a pharmaceutically acceptable salt thereof.

Suitable examples of groups A and B include:

(i) A is -N=C=O and B is $-NHR^{3'}$,
(ii) A is $-NR^{2'}COL$ and B is $-NHR^{3'}$,
(iii) A is $-NHR^{2'}$ and B is $NR^{3'}COL$,
(iv) A is $NHR^{2'}$ and B is -N=C=O or
(v) A is halogen and B is $-NR^{3'}CONHR^{2'}$

wherein $R^{2'}$ and $R^{3'}$ are as defined above and L is a leaving group. Examples of suitable leaving groups L include halogen such as chloro, bromo, imidazole or phenoxy or phenylthio optionally substituted for example with halogen.

When A is -N=C=O and B is $NHR^{3'}$ or when A is $NHR^{2'}$ and B is -N=C=O the reaction is suitably carried out in an inert solvent for example dichloromethane or toluene at ambient temperature. When A is $-NR^{2'}COL$ and B is $NHR^{3'}$ or when A is $-NHR^{2'}$ and B is $-NR^{3'}COL$, the reaction is suitably carried out in an inert solvent such as dichloromethane at ambient temperature optionally in the presence of a base, such as triethylamine or in dimethylformamide at ambient or elevated temperature. When A is halogen and B is $NR^{3'}CONHR^{2'}$, the reaction is suitably carried out in an inert solvent such as toluene at elevated temperature, optionally in the presence of a base.

Suitable examples of groups $R^{1'}$ and $R^{4'}$, which are convertible to R^1 and R^4 alkyl groups respectively, include acyl groups which are introduced conventionally and may be converted to the corresponding alkyl group by conventional reduction, such as using sodium borohydride in an inert solvent followed by hydrogenolysis in an inert solvent. Hydrogen substituents may be obtained from alkoxycarbonyl groups which may be converted to hydrogen by hydrolysis and decarboxylation.

Interconversions of R^1, R^2, R^3 and R^4 are carried out by conventional procedures. For example, in the case wherein R^2 is C_{1-6} alkyl and R^3 is hydrogen it is possible to introduce a C_{1-6} alkyl group at the R^3 position by conventional alkylation using 1 molar equivalent of a C_{1-6} alkyl halide and 1 molar equivalent of a suitable base in an inert solvent. Suitable examples of a group $R^{2'}$ and $R^{3'}$ which is convertible to R^2 and R^3,

include alkoxycarbonyl and benzyl or *para*-methoxybenzyl which are converted to R^2 and R^3 is hydrogen using conventional conditions.

R^1 halo and R^4 halo may be introduced by selective halogenation of the ring P or the benzene ring respectively using conventional conditions.

It should be appreciated that it may be necessary to protect any R^1 to R^7 hydrogen variables which are not required to be interconverted. Suitable protecting groups are described in 'Protective groups in organic synthesis' Greene T.W., New York, Wiley (1981). It should be appreciated that it is preferred that groups R^1 to R^7 are introduced before coupling compounds of formula (II) and (III).

Compounds of formula (II) in which A is $NHR^{2'}$ are known compounds or can be prepared analogously to known compounds. see, for example, WO 92/05170 (SmithKline Beecham plc). Compounds of formula (II) in which A is -N=C=O may be prepared by treating a compound of formula (II) in which :

i) A is amino, with phosgene or a phosgene equivalent, in the presence of excess base in an inert solvent.

ii) A is acylazide (i.e. CON_3), via the nitrene, by thermal rearrangement using conventional conditions (ref L.S. Trifonov et al, Helv. Chim. Acta 1987 70 262).

iii) A is $CONH_2$, via the nitrene intermediate using conventional conditions.

Examples of phosgene equivalents include triphosgene, carbonyldiimidazole, phenyl chloroformate and phenyl chorothioformate. Compounds of formula (II) in which A is $NR_2'COL$ may be prepared by reacting a compound of formula (II) in which A is NHR_2' with phosgene or a phosgene equivalent in an inert solvent, at low temperature, if necessary in the presence of one equivalent of a base such as trithylamine. Compounds of formula (II) in which A is halogen and R_4' is hydrogen are commercially available.

Compounds of formula (III) are commercially available or may be prepared according to analogous methods to those outlined above for compounds of formula (II).

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative. N-oxides may be formed conventionally by reaction with hydrogen peroxide or percarboxylic acids.

The following Examples illustrate the preparation of compounds of the invention.

Found: C, 70.32: H, 5.67; N, 13.44%
$C_{18}H_{17}N_3O_2$ requires C. 70.34; H. 5.58: N. 13.67%
Found: M^+ 307 $C_{18}H_{17}N_3O_2$ requires 307

Example 6
N-(3-Dimethylaminophenyl)-N'-(2-methyl-4-quinolinyl) urea

1,1'-Carbonyldiimidazole (0.26g, 1.6 mmol), was added portionwise to a solution of 4-aminoquinaldine (0.23g, 1.47 mmol) in dry dichloromethane (15 ml), under a nitrogen atmosphere. After 1/2h, at room temperature, the solvent was evaporated off and the residue was taken up in DMF (5 ml). After addition of 3-(dimethylamino)aniline (0.2g, 1.47 mmol) in DMF (10ml), the reaction mixture was heated at 90°C for 1h. Addition of water after cooling to room temperature, gave the crude product as a precipitate, which was collected and dried in vacuo. Purification by column chromatography on silica gel, using dichloromethane as eluant gave the title compound (0.16g, 34%) as a light brown solid, m.p. 167-171°C.

NMR (D_6-DMSO) δ: 2.6 (3H, s), 2.91 (6H, s), 6.42 (1H, m), 6.77 (1H, m), 6.98 (1H, s), 7.12 (1H, t, J 6), 7.59 (1H, t, J 3), 7.72 (1H, t, J 6), 7.89 (1H, d, J 6), 8.12 (2H, m), 9.10 (1H, s), 9.19 (1H, s).

Found: M^+ 320 $C_{19}H_{20}N_4O$ requires 320

Example 7
N-(3-Methoxyphenyl)-N'-(2-methyl-4-quinolinyl) urea

3-Methoxyphenyl isocyanate (0.83 ml, 6.3 mmol) in dry dichloromethane (30 ml) was added slowly to 4-aminoquinaldine (1g, 6.3 mmol) in dry toluene (30 ml) under a nitrogen atmosphere, and left to stir at room temperature for 19h. The precipitate which formed was filtered off, washed with cold 1:1 toluene/dichloromethane and dried in vacuo. The crude product was purified by recrystallization from ethanol to give the title compound (0.99g, 51%) as a white solid, m.p. 191-193°C.

NMR (D_6-DMSO) δ: 2.6 (3H, s), 3.77 (3H, s), 6.62 (1H, m), 6.99 (1H, d, J 6), 7.22-7.28 (2H, m), 7.61 (1H, t, J 3), 7.72 (1H, t, J 3), 7.89 (1H, d, J 6), 8.14 (2H, m), 9.18 (1H, s), 9.35 (1H, s).

Found: M^+ 307 $C_{18}H_{17}N_3O_2$ requires 307

Example 8
N-(3-Ethoxycarbonylphenyl)-N'-(2-methyl-4-quinolinyl) urea

3-Ethoxycarbonylphenyl isocyanate (1g, 5.2 mmol) in dry dichloromethane (30 ml), was added slowly to 4-aminoquinaldine (0.83g, 5.2 mmol) in dry toluene (30 ml), under a nitrogen atmosphere, and left to stir at room temperature for 19h. The precipitate which formed was filtered off, washed with cold 1:1 toluene/dichloromethane and dried in vacuo. The crude product was chromatographed on silica gel, using dichloromethane as the eluant to give the title compound (0.78g, 43%) as white crystals, m.p. 165-170°C.

NMR (D_6-DMSO) δ: 1.32 (3H, t, J 3), 2.6 (3H, s), 4.33 (2H, q, J 6), 7.48 (1H, t, J 6), 7.59-7.75 (4H, m), 7.9 (1H, d, J 6), 8.12 (2H, m), 8.22 (1H, s), 9.18 (1H, s), 9.57 (1H, s).

Found: M^+ 349 $C_{20}H_{19}N_3O_3$ requires 349

Example 9
N-(2-Methyl-4-quinolinyl)-N'-(3-tifluoromethylphenyl) urea

α,α,α- Trifluoro-m-tolyl isocyanate (0.96 ml, 6.33 mmol) in dry dichloromethane (30 ml) was added slowly to 4-amino-quinaldine (1g, 6.33 mmol) in dry toluene (30 ml), under a nitrogen atmosphere. Following the procedure described in Example 4, gave the title compound (0.18g, 85%) as a white powder, m.p. 165-170°C.

NMR (D_6-DMSO) δ: 2.58 (3H, s), 7.37 (1H, m), 7.55-7.61 (3H, m), 7.7 (1H, t J 6), 7.87 (1H, d, J 8), 8.10 (3H, m), 9.22 (1H, s), 9.60 (1H, s).

Found: M^+ 345 $C_{18}H_{14}N_3O\,F_3$ requires 345

Example 10
N-(Phenyl)-N'-(3-quinolinyl) urea

Phenyl isocyanate (0.75 ml, 7 mmol) in dry dichloromethane (30 ml) was added slowly to 3 aminoquinoline (1g, 7 mmol) in dry toluene (30 ml) under a nitrogen atmosphere. Following the procedure described in Example 7, gave the title compound (1.18g, 65%) as a white powder, m.p. 289-290°C.

NMR (D_6-DMSO) δ: 7.0 (1H, t, J 6), 7.30 (2H, t, J 8), 7.49-7.61 (4H, m), 7.88-7.97 (2H, m), 8.54 (1H, d, J 3), 8.82 (1H, d, J 3), 8.92 (1H, s), 9.14 (1H, s).

Found: C, 72.78; H, 5.13; N, 15.98%
$C_{16}H_{13}N_3O$ requires C, 72.99; H, 4.98; N, 15.96%
Found: M^+ 263 $C_{16}H_{13}N_3O$ requires 263

Example 11

N-(3-Chloro-4-methylphenyl)-N'-(3-pyridyl) urea hydrochloride

Nicotinoyl azide (0.40g, 2.7 mmol) was stirred at reflux under nitrogen atmosphere in dry toluene (10 ml) for 1h, with gas evolution. The solution was cooled to ambient temperature, and 3-chloro-4-methylaniline (0.30 ml, 2.4 mmol) was added. The suspension so formed was stirred for 1h, when the solid was filtered off, washed with 1:1 toluene/dichloromethane, and dried **in vacuo** at 70°C. This gave the free base of the title compound (0.64g, 85%) as a white solid.

NMR (D_6-DMSO) δ: 2.25 (3H, s), 7.23 (2H, m), 7.31 (1H, m), 7.70 (1H, s), 7.93 (1H, m,), 8.18 (1H, d, J 4), 8.59 (1H, d, J 2), 8.90 (2H, 2xs).

N-(3-Chloro-4-methyl)-N'-(3-pyridyl) urea (0.55g, 2.1 mmol) was dissolved in hot ethanol (10 ml), and a solution of hydrogen chloride in ether (ca. 0.9M, 2.5 ml, ca. 2.3 mmol) was added. The suspension was cooled to ambient temperature, and the solid was filtered off, washed with cold ethanol, and dried **in vacuo** at 70°C. This gave the title compound (0.62g, 76%) as a white solid, m.p. 214.5-216°C.

NMR (D_6-DMSO) δ: 2.25 (3H, s), 7.25 (2H, m), 7.68 (1H, s), 7.92 (1H, dd, J 8, 5), 8.33 (1H, d, J 8), 8.49 (1H, d), 9.07 (1H, s), 9.79 (1H, s), 10.37 (1H, s).

Found: C, 51.4; H, 4.5; N, 14.5%
$C_{13}H_{12}ClN_3O$. HCl. $0.25H_2O$ requires C, 51.6; H, 4.5; N, 13.9%
Found: M^+ 261, 263. $C_{13}H_{12}ClN_3O$ requires 261, 263.

Example 12

N-(3-Chloro-4-methylphenyl)-N'-(4-pyridyl) urea hydrochloride

3-Chloro-4-methylaniline (0.65 ml, 5.3 mmol) was stirred under nitrogen in

dichloromethane (15 ml) at 0°C as triethylamine (0.82 ml, 5.9 mmol) was added. To this mixture was then added phosgene in toluene solution (1.93M, 4.1 ml, 7.9 mmol). After stirring at 0°C for 0.5h, triethylamine (1.6 ml, 11.8 mmol) was added and, after a further 0.5h, 4-aminopyridine (0.50g, 5.3 mmol) was added. The mixture was stirred at ambient temperature for 16h, and then treated with sodium hydroxide solution (5M, ca. 1 ml). After 0.5h, it was diluted with water (50 ml) and dichloromethane (50 ml), and the precipitate was filtered off, washed with water, and dried **in vacuo** at 70°C. This gave the free base of the title compound (1.03g, 74%) as a white solid.

NMR (D_6-DMSO) δ: 2.25 (3H, s), 7.23 (2H, m), 7.41 (2H, d, J 5), 7.67 (1H, s),8.35 (2H, d, J 5) 8.99 (1H, s), 9.18 (1H, s).

N-(3-Chloro-4-methylphenyl)-N'-(4-pyridyl) urea (1.03g, 3.9 mmol) was treated with hydrogen chloride using the method of Example 11. This gave the title compound (0.95g, 81%) as a white solid, m.p. 235-240°C (decomp.).

NMR (D_6-DMSO) δ: 2.27 (3H, s), 7.28 (2H, m), 7.67 (1H, s), 7.89 (2H, d, J 6), 8.60 (2H, d, J 6), 10.09 (1H, s), 11.27 (1H, s).

Found: C, 50.6; H, 4.4; N, 13.7%

$C_{13}H_{12}ClN_3O.HCl$. 0.59 H_2O requires C, 50.6; H, 4.6; N, 13.6%

Found: M^+ 261, 263 $C_{13}H_{12}ClN_3O$ requires 261, 263.

Example 13

N-(3-Pyridyl)-N'-(3-(trifluoromethyl)phenyl)urea

The title compound was prepared in 91% yield from 3-pyridyl isocyanate and 3-aminobenzotrifluoride; m.p. 180-184° C.

NMR (DMSO-d_6) δ: 7.3 (2H, m), 7.55 (2H, m), 7.95 (1H, d, J 8), 8.0 (1H, s), 8.2 (1H, d, J 4), 8.6 (1H, d, J 2), 9.0 (1H, s), 9.2 (1H, s).

Example 14

N-(3-Methylphenyl)-N'-(3-pyridyl)urea hydrochloride

The title compound was prepared in 87% yield from 3-aminopyridine and m-tolyl isocyanate, followed by salt formation with HCl; m.p. 182-183° C.

NMR (DMSO-d_6) δ: 2.3 (3H, s), 6.85 (1H, d, J 7), 7.2 (1H, t, J 8), 7.3 (2H, m), 7.9 (1H, dd, J 8,5), 8.3 (1H, m), 8.5 (1H. d, J 5), 9.1 (1H, d, J 2), 9.5 (1H, s), 10.35 (1H, s).

Example 15
N-(4-Chlorophenyl)-N'-(3-pyridyl)urea

The title compound was prepared in 29% yield from 3-aminopyridine, 1,1'-carbonyldiimidazole and 4-chloroaniline; m.p. 207-209° C

NMR (DMSO-d_6) δ: 7.3 (3H, m), 7.5 (2H, d, J 9), 7.95 (1H, m), 8.2 (1H, m), 8.6 (1H, d, J 2), 8.9 (1H, s), 9.0 (1H, s)

Example 16
N-(3-Chlorophenyl)-N'-(3-pyridyl)urea

The title compound was prepared in 86% yield from 3-aminopyridine and 3-chlorophenyl isocyanate; m.p. 185-187° C

NMR (DMSO-d_6) δ: 7.0 (1H, m), 7.3 (3H, m), 7.7 (1H, s), 7.95 (1H, m), 8.2 (1H, m), 8.6 (1H, d, J 2), 8.95 (1H, s), 9.05 (1H, s)

Example 17
N-(3-Hydroxyphenyl)-N'-(2-methyl-4-quinolinyl)urea

The title compound was prepared in 19% yield from 4-amino-2-methylquinoline, 1,1'-carbonyldiimidazole and 3-aminophenol; m.p. 224-225° C

NMR (DMSO-d_6) δ: 2.6 (3H, s), 6.45 (1H, m), 6.9 (1H, d, J 7), 7.1 (2H, m), 7.6 (1H, t, J 7), 7.7 (1H, t, J 7), 7.9 (1H, d, J 7), 8.15 (2H, m), 9.2 (1H, b), 9.3 (1H, s), 9.45 (1H, s)

Example 18
N-(3-Bromophenyl)-N'-(3-pyridyl)urea

The title compound was prepared in 75% yield from 3-bromopyridine and 3-pyridyl isocyanate; m.p. 190-193° C.

NMR (DMSO-d_6) δ: 7.10-7.40 (4H, m), 7.86 (1H, s), 7.94 (1H, m), 8.22 (1H, d, J=5Hz), 8.62 (1H, d. J=2Hz), 8.93 (1H, s), 9.02 (1H, s).

Example 19
N-(3,4-Dichlorophenyl)-N'-(3-pyridyl)urea

The title compound was prepared in 65% yield from 3,4-dichloroaniline and 3-pyridyl isocyanate; m.p. 206° C-210° C.

NMR (DMSO-D_6) δ: 7.25-7.42 (2H, m), 7.50 (1H, d, J=7Hz), 7.83-7.90 (2H, m), 8.23 (1H, d, J=3Hz), 8.62 (1H, d, J=1Hz), 8.98 (1H, s), 9.23 (1H, s)

Example 20
N-(3-Fluoro-4-methylphenyl)-N'-(3-pyridyl)urea

The title compound was prepared in 85% yield from 3-fluoro-4-methylaniline and 3-pyridyl isocyanate; m.p. 190-191° C.

NMR (DMSO-D_6) δ: 7.02-7.48 (4H, m), 7.94 (1H, m), 8.19 (1H, m), 8.59 (1H, m), 8.87 (1H, s), 8.92 (1H, s)

Example 21
N-(4-Ethoxycarbonylphenyl)-N'-(3-pyridyl)urea

The title compound was prepared in 83% yield from ethyl 4-aminobenzoate and 3-pyridyl isocyanate: m.p. 156-160° C

NMR (DMSO-D_6) δ: 1.32 (3H, t, J=7.5Hz), 4.30 (2H, q, J=7.5Hz), 7.34 (1H, dd, J=7Hz & 4Hz), 7.60 (2H, m), 7.86-8.02 (3H, m), 8.21 (1H, m), 8.63 (1H, m), 8.96 (1H, s), 9.24 (1H, s)

Example 22
N-(3-Chloro-4-methoxycarbonylphenyl)-N'-(3-pyridyl)urea

The title compound was prepared in 30% yield from methyl 4-amino-2-chlorobenzoate and 3-pyridyl isocyanate m.p. 170-171° C

NMR (DMSO-D_6) δ: 3.82 (3H, s), 7.30 (2H, m), 7.78-8.00 (3H, m), 8.25 (1H, m), 8.64 (1H, m), 9.08 (1H, s), 9.39 (1H, s)

Example 23
N-(3-Bromo-4-methylphenyl)-N'-(3-pyridyl)urea

The title compound was prepared in 61% yield from 3-bromo-4-methylaniline and 3-pyridyl isocyanate; m.p. 168-171° C

NMR (DMSO-D_6) δ: 2.28 (3H, s), 7.21-7.39 (3H, m), 7.83-8.00 (2H, m), 8.20 (1H, m), 8.61 (1H, m), 8.89 (2H, m)

Example 24
N-(3-Chloro-4-cyanophenyl)-N'-(3-pyridyl)urea

The title compound was prepared in 22% yield from 4-amino-2-chlorobenzonitrile and 3-pyridyl isocyanate; m.p. 262-264° C

NMR (DMSO-D_6) δ: 7.28-7.56 (2H, m), 7.80-8.06 (3H, m), 8.26 (1H, m), 8.64 (1H, s), 9.17 (1H, s), 9.54 (1H, s)

Example 25
N-(4-Nitro-3-trifluoromethylphenyl)-N'-(3-pyridyl)urea

The title compound was prepared in 31% yield from 4-nitro-3-trifloromethylaniline and 3-pyridyl isocyanate; m.p. 214-216° C

NMR (DMSO-D_6) δ: 7.37 (1H, dd, J=7Hz & 4Hz), 7.87 (1H, m, J=7Hz), 7.97 (1H, m, J=7Hz), 8.14-8.29 (3H, m), 8.67 (1H, m), 9.22 (1H, s), 9.81 (1H, s)

Example 26
N-(4-Chloro-3-trifluoromethylphenyl)-N'-(3-pyridyl)urea

The title compound was prepared in 48% yield from 4-chloro-3-trifluoromethylaniline and 3-pyridyl isocyanate; m.p. 196-199° C.

NMR (DMSO-D_6) δ: 7.33 (1H, dd, J=7Hz & 4Hz), 7.59-7.71 (2H, m), 7.95 (1H, m), 8.10 (1H, m), 8.22 (1H, m), 8.63 (1H, m), 9.04 (1H, s), 9.32 (1H, s)

Example 27
N-(3-Chloro-4-carboxyphenyl)-N'-(3-pyridyl)urea

The title compound was prepared in 86% yield from 4-amino-2-chlorobenzoic acid and 3-pyridyl isocyanate; m.p. 170-175° C

NMR (DMSO-D_6) δ: 7.41 (2H, m), 7.76-7.88 (2H, m), 7.99 (1H, d, J=7Hz), 8.25 (1H, br s), 8.68 (1H, br s), 9.13 (1H, s), 9.37 (1H, s)

Example 28
N-(2-Methoxy-4-trifluoromethylphenyl)-N'-(3-pyridyl)urea

The title compound was prepared in 91% yield from 2-methoxy-4-trifluoromethyl-aniline and 3-pyridyl isocyanate; m.p. 210° C

NMR (DMSO-D_6) δ: 4.00 (3H, s), 7.16-7.45 (3H, m), 7.98 (1H, m, J=7Hz), 8.23 (1H, m), 8.48-8.74 (3H, m), 9.60 (1H, s)

Example 29
N-(2,3-Dichlorophenyl)-N'-(2-methyl-4-quinolinyl)urea

The title compound was prepared in 22% yield from 2,3-dichloroaniline and 2-methyl-4-quinolinyl isocyanate; m.p. 125-127° C

NMR (DMSO-D_6) δ: 2.62 (3H. s), 7.34-7.46 (2H, m), 7.63 (1H. t, J=7Hz), 7.76 (1H, t, J=7Hz), 7.94 (1H. t, J=7Hz), 8.12-8.31 (3H, m), 9.27 (1H, s), 9.83 (1H, s)

Example 30

N-(3-Chloro-4-ethylphenyl)-N'-(3-pyridyl)urea

The title compound was prepared in 85% yield from 3-chloro-4-ethylaniline & 3-pyridyl isocyanate; m.p. 193-196° C.

NMR (DMSO-d_6) δ: 1.16 (3H, t, J=5Hz), 2.64 (2H, q, J=5Hz), 7.20-7.40 (3H, m), 7.67 (1H, s), 7.94 (1H, m), 8.20 (1H, d, J=2Hz), 8.60 (1H, d, J=0-1Hz), 8.90 (2H, d, J=5Hz).

Example 31

N-(3-Chloro-4-propylphenyl)-N'-(3-pyridyl)urea

The title compound was prepared in 78% yield from 3-Chloro-4-propylaniline & 3-pyridyl isocyanate; m.p. 184-186° C

NMR (DMSO-D_6) δ: 0.91 (3H, t, J=5Hz), 1.56 (2H, q, J=5Hz), 2.60 (2H, t, J=5Hz), 7.20-7.35 (3H, m), 7.68 (1H, s), 7.94 (1H, m), 8.19 (1H, d, J=2Hz), 8.59 (1H, d, J=0-1Hz), 8.92 (2H, d, J=5Hz).

Example 32

N-(3-Chloro-4-tert-butylphenyl)-N'-(3-pyridyl)urea

The title compound was prepared in 73% yield from 3-chloro-4-tert-butylaniline & 3-pyridyl isocyanate; m.p. 190° C-193° C.

NMR (DMSO-D_6) δ: 1.42 (9H, s), 7.20-7.40 (3H, m), 7.66 (1H, d, J=2Hz), 7.93 (1H, m), 8.19 (1H, d, J=5Hz), 8.60 (1H, d, J=2Hz), 8.90 (2H, d, J=11Hz)

Example 33

N-(3-Hydroxy-4-(methoxycarbonyl)phenyl)-N'-(3-pyridyl)urea

N-(3-Hydroxy-4-carboxyphenyl)-N'-(3-pyridyl)urea was prepared in 69% yield from 4-aminosalicylic acid and 3-pyridyl isocyanate in DMF/toluene. This material (0.37g, 1.4 mmol) was then stirred in methanol (20 ml) as thionyl chloride (2 ml) was cautiously added. The suspension was stirred at reflux under argon for 2 days, and evaporated to dryness. The residue was suspended in saturated sodium hydrogen carbonate solution, and the solid was filtered off, washed with water, dried, and recrystallised from ethanol/petroleum ether (b.p. 60-80° C), giving the title compound (0.16g, 41%) as a white solid. m.p. 199-200° C.

NMR (DMSO d_6) δ :

3.88 (3H, s), 6.98 (1H, dd, J 8, 2), 7.27 (1H, d, J 2), 7.34 (1H, dd, J 8, 5), 7.73 (1H, d, J 9), 7.96 (1H, m), 8.24 (1H, d, J 4), 8.63 (1H, d, J 2), 9.04 (1H, s), 9.27 (1H, s), 10.69 (1H, s).

Pharmacological data

[^{3}H]-mesulergine binding to rat 5-HT$_{2C}$ clones expressed in 293 cells in vitro

Evidence from the literature suggests that 5-HT$_{2C}$ antagonists may have a number of therapeutic indications including the treatment of anxiety, migraine, depression, feeding disorders and obsessive compulsion disorders. (Curzon and Kennett, 1990; Fozard and Gray, 1989) and Alzheimer's Disease (Lawlor, 1989, J. Arch. Gen. Psychiat. Vol. 46 p.542).

The affinity of test drugs for the 5-HT$_{2C}$ binding site can be determined by assessing their ability to displace [^{3}H]-mesulergine from 5-HT$_{2C}$ clones expressed in 293 cells (Julius *et al.*, 1988). The method employed was similar to that of Pazos et al, 1984.

The cells suspension (50ml) was incubated with [^{3}H]-mesulergine (0.5nM) in Tris HCl buffer (pH 7.4) at 37°C for 30 minutes. Non-specific binding was measured in the presence of mianserin (10^{-6}M). Ten concentrations of test drug (3×10^{-9} to 10^{-4}M final concentration) were added in a volume of 50ml. The total assay volume was 500ml. Incubation was stopped by rapid filtration using a Brandel cell harvester and radioactivity measured by scintillation counting. The IC$_{50}$ values were determined using a four parameter logistic program (DeLean 1978) and the pK$_i$ (the negative logarithm of the inhibition constant) calculated from the Cheng Prusoff equation where:

$$K_i = \frac{IC_{50}}{1 + \frac{C}{Kd}}$$

K_i = inhibition constant.

C = concentration of [^{3}H]-mesulergine

Kd = Affinity of mesulergine for 5-HT$_{1C}$ binding sites.

Curzon, G.A. and Kennett, G.A. (1990). TIPS, Vol. 11, 181-182.

Fozard, J.R. and Gray, J.A. (1989). TIPS, Vol. 10, 307-309.

Pazos, A. *et al.* (1984). Eur. J. Pharmacol., 106, 531-538.

Julius *et al.* (1988) Science 241, 558-564

DeLean A, Munson P.J., Rodbaud D (1978) Am. J. Physiol 235, E97-E102.

Results

The compound of Example 7 has a pKi of 8.28.

The compound of Example 11 has a pKi of 7.79.

Reversal of MCPP-induced Hypolocomotion

Administration of m-(chlorophenyl)piperazine (mCPP) to rats induces hypolocomotion (Kennett and Curzon 1988, Luckie *et al.* 1989) as seen with the related drug 1-(m-trifluoromethylphenyl)piperazine (TFMPP) (Lucki and Frazer 1982, Kennett and Curzon 1988). This effect was blocked by the non specific 5-HT_{2C}/5-HT_{2A} receptor antagonists mianserin, cyproheptadine and metergoline and perhaps by mesulergine. It was not blocked by the 5-HT_2 receptor antagonists ketanserin and ritanserin at relevant doses (Kennett and Curzon 1991) nor by antagonists of 5-HT_{1A}, 5-HT_{1B}, 5-HT_3, α_2 adrenoceptors or dopamine D_2 receptors. The effect of mCPP is therefore considered to be mediated by 5-HT_{2C} receptors (Kennett and Curzon 1988) as confirmed by subsequent studies (Lucki *et al.*, 1989). Since mCPP causes hypolocomotion when infused into the cerebral ventricles this effect is probably centrally mediated (Kennett and Curzon 1988).

mCPP-induced hypolocomotion was measured in automated locomotion cages of dimensions 56 cm long x 16½ cm wide x 25 cm high and made of black perspex. Two photobeams traversed the width of the cages at either end at ground level. Sequential breaking of these beams allowed the measurement of cage transits.

Male Sprague Dawley rats (200-250g) (Charles River) were housed in groups of six. They were given drugs orally 1h pretest and 40 mins later mCPP (7 mg/kg i.p.). After a further 20 min they were placed in individual automated cages in groups of four under red light in an adjacent room. After 10 min the test was terminated. Reversal of mCPP-induced hypolocomotion was considered as evidence of *in vivo* central 5-HT_{2C} receptor antagonist properties.

Kennett, G.A., Curzon, G., (1988). Brit. J. Pharmacol. **94**, 137-147.

Kennet G.A., Curzon, G., (1991). Brit.J. Pharmacol. **103**, 2016-2020.

Lucki, I., Frazer, A., (1982) Am. Soc. Neurosci. 8(abstr.), 101.

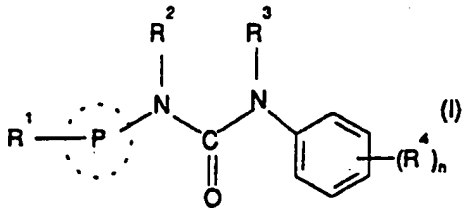
Lucki, I., Ward, M.R., Frazer, A., (1989). J.Pharmacol. Exp. Therap. **249**, 155-164.

Result

The compound of Example 11 had an ID_{50} of 78 mg/kg p.o.

CLAIMS

1. Use of a compound of formula (I) or a salt thereof:



(I)

wherein:

P represents a quinoline or isoquinoline residue or a 5- or 6-membered aromatic heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur;

R^1 is hydrogen, C_{1-6} alkyl, halogen, NR^5R^6 or OR^7 where R^5, R^6 and R^7 are independently hydrogen or C_{1-6} alkyl;

R^2 and R^3 are independently hydrogen or C_{1-6} alkyl;

R^4 is hydrogen, C_{1-6} alkyl, CF_3, nitro, cyano, acyl, halogen, NR^5R^6, OR^7 or CO_2R^7 where R^5, R^6 and R^7 are independently hydrogen or C_{1-6} alkyl as defined for R^1; and

n is 1, 2 or 3,

in the manufacture of a medicament for the treatment or prophylaxis of CNS disorders.

2. Use according to claim 1 in which P is pyridyl or quinolyl.

3. Use according to claim 1 or 2 in which R^1 is hydrogen or methyl.

4. Use according to any one of claims 1 to 3 in which R^2 and R^3 are hydrogen.

5. Use according to any one of claims 1 to 4 in which P is pyridyl or quinolyl.

6. Use according to claim 1 in which the compound of formula (I) is selected from:

N-(Phenyl)-N'-(2-methyl-4-quinolinyl) urea,

N-(6-Quinolinyl)-N'-(3-trifluoromethylphenyl) urea,

N-(3-Dimethylaminophenyl)-N'-(6-quinolinyl) urea,

N-(Phenyl)-N'-(6-quinolinyl) urea,

N-(4-Methoxyphenyl)-N'-(2-methyl-4-quinolinyl) urea,

N-(3-Dimethylaminophenyl)-N'-(2-methyl-4-quinolinyl) urea,

N-(3-Methoxyphenyl)-N'-(2-methyl-4-quinolinyl) urea,

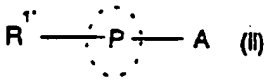
N-(3-Ethoxycarbonylphenyl)-N'-(2-methyl-4-quinolinyl) urea,
N-(2-Methyl-4-quinolinyl)-N'-(3-trifluoromethylphenyl) urea ,
N-(Phenyl)-N'-(3-quinolinyl) urea,
N-(3-Chloro-4-methylphenyl)-N'-(3-pyridyl) urea,
N-(3-Chloro-4-methylphenyl)-N'-(4-pyridyl) urea,
N-(3-Pyridyl)-N'-(3-(trifluoromethyl)phenyl)urea,
N-(3-Methylphenyl)-N'-(3-pyridyl)urea,
N-(4-Chlorophenyl)-N'-(3-pyridyl)urea,
N-(3-Chlorophenyl)-N'-(3-pyridyl)urea,
N-(3-Hydroxyphenyl)-N'-(2-methyl-4-quinolinyl)urea,
N-(3-Bromophenyl)-N'-(3-pyridyl)urea,
N-(3,4-Dichlorophenyl)-N'-(3-pyridyl)urea,
N-(3-Fluoro-4-methylphenyl)-N'-(3-pyridyl)urea,
N-(4-Ethoxycarbonylphenyl)-N'-(3-pyridyl)urea,
N-(3-Chloro-4-methoxycarbonylphenyl)-N'-(3-pyridyl)urea,
N-(3-Bromo-4-methylphenyl)-N'-(3-pyridyl)urea,
N-(3-Chloro-4-cyanophenyl)-N'-(3-pyridyl)urea,
N-(4-Nitro-3-trifluoromethylphenyl)-N'-(3-pyridyl)urea,
N-(4-Chloro-3-trifluoromethylphenyl)-N'-(3-pyridyl)urea,
N-(3-Chloro-4-carboxyphenyl)-N'-(3-pyridyl)urea,
N-(2-Methoxy-4-trifluoromethylphenyl)-N'-(3-pyridyl)urea,
N-(3-Chloro-4-ethylphenyl)-N'-(3-pyridyl)urea,
N-(3-Chloro-4-propylphenyl)-N'-(3-pyridyl)urea,
N-(3-Chloro-4-tert-butylphenyl)-N'-(3-pyridyl)urea,
N-(3-Hydroxy-4-(methoxycarbonyl)phenyl)-N'-(3-pyridyl)urea
or a pharmaceutically acceptable salt thereof.

7. A compound of formula (I) which is:
N-(Phenyl)-N'-(2-methyl-4-quinolinyl) urea,
N-(6-Quinolinyl)-N'-(3-trifluoromethylphenyl) urea,
N-(3-Dimethylaminophenyl)-N'-(6-quinolinyl) urea,
N-(Phenyl)-N'-(6-quinolinyl) urea,
N-(4-Methoxyphenyl)-N'-(2-methyl-4-quinolinyl) urea,
N-(3-Dimethylaminophenyl)-N'-(2-methyl-4-quinolinyl) urea,
N-(3-Methoxyphenyl)-N'-(2-methyl-4-quinolinyl) urea,
N-(3-Ethoxycarbonylphenyl)-N'-(2-methyl-4-quinolinyl) urea
N-(2-Methyl-4-quinolinyl)-N'-(3-trifluoromethylphenyl) urea ,
N-(Phenyl)-N'-(3-quinolinyl) urea,

N-(3-Chloro-4-methylphenyl)-N'-(3-pyridyl) urea,
N-(3-Chloro-4-methylphenyl)-N'-(4-pyridyl) urea,
N-(3-Pyridyl)-N'-(3-(trifluoromethyl)phenyl)urea,
N-(3-Methylphenyl)-N'-(3-pyridyl)urea,
N-(4-Chlorophenyl)-N'-(3-pyridyl)urea,
N-(3-Chlorophenyl)-N'-(3-pyridyl)urea,
N-(3-Hydroxyphenyl)-N'-(2-methyl-4-quinolinyl)urea,
N-(3-Bromophenyl)-N'-(3-pyridyl)urea,
N-(3,4-Dichlorophenyl)-N'-(3-pyridyl)urea,
N-(3-Fluoro-4-methylphenyl)-N'-(3-pyridyl)urea,
N-(4-Ethoxycarbonylphenyl)-N'-(3-pyridyl)urea,
N-(3-Chloro-4-methoxycarbonylphenyl)-N'-(3-pyridyl)urea,
N-(3-Bromo-4-methylphenyl)-N'-(3-pyridyl)urea,
N-(3-Chloro-4-cyanophenyl)-N'-(3-pyridyl)urea,
N-(4-Nitro-3-trifluoromethylphenyl)-N'-(3-pyridyl)urea,
N-(4-Chloro-3-trifluoromethylphenyl)-N'-(3-pyridyl)urea,
N-(3-Chloro-4-carboxyphenyl)-N'-(3-pyridyl)urea,
N-(2-Methoxy-4-trifluoromethylphenyl)-N'-(3-pyridyl)urea,
N-(3-Chloro-4-ethylphenyl)-N'-(3-pyridyl)urea,
N-(3-Chloro-4-propylphenyl)-N'-(3-pyridyl)urea,
N-(3-Chloro-4-tert-butylphenyl)-N'-(3-pyridyl)urea,
N-(3-Hydroxy-4-(methoxycarbonyl)phenyl)-N'-(3-pyridyl)urea
or a pharmaceutically acceptable salt thereof.

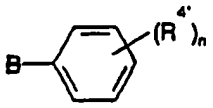
8. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof which comprises:

the coupling of a compound of formula (II);



(II)

with a compound of formula (III);



(III)

wherein P is as defined in relation to formula (I), A and B contain the appropriate

functional group(s) necessary to form the moiety, $-NR^{2'}CONR^{3'}$ when coupled, the variables $R^{1'}$, $R^{2'}$, $R^{3'}$, and $R^{4'}$ are R^1, R^2, R^3, and R^4 respectively, as defined in formula (I), or groups convertible thereto, and thereafter optionally and as necessary and in any appropriate order, converting any $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$, when other than R^1, R^2, R^3 and R^4 respectively to R^1, R^2, R^3 and R^4, interconverting R^1, R^2, R^3, and R^4 and forming a pharmaceutically acceptable salt thereof.